REMARKS

Entry of the foregoing and favorable reconsideration of the subject application in light of the following remarks are respectfully requested.

Claims 60, 62, 63, 64, 65, 66, 67, 68, 69, and 70 are pending in this case. All pending claims were rejected in the Official Action under 35 U.S.C. § 112, ¶1 and 35 U.S.C. § 102(e). Regarding the rejection of the claims under 35 U.S.C §112, the Applicants have amended claims 60, 62, 63, and 64 to further clarify applicant's invention, in accordance with the Examiner's suggestion. In view of the amendment, the rejection under 35 U.S.C § 112, is rendered moot. Support for this amendment can be found, for example, on page 5, lines 5-9, of the specification. Accordingly, no new matter was added by way of this amendment. Due to the renumbering of the claims, dependent claims 64 to 70 were also amended to properly depend from the appropriate claim(s). Further, claims 65, 66, 67, 68, and 70 were amended to claim more distinctly and clearly the subject matter of applicant's invention. No new matter was added by way of these amendments.

In the Official Action, claims 60 to 70 were also rejected under 35 U.S.C. § 102(e), as allegedly being anticipated by Sherman (WO 96/17598). The rejection is respectfully traversed.

To anticipate a claim, a prior art document must expressly or inherently disclose each and every element of the claimed invention. As discussed further below, Sherman not only fails to disclose, either expressly or inherently, each element of the present invention, but does not even remotely suggest the inventive aspects of applicant's claimed invention. Specifically, the present

invention is directed to a long lag pellet suitable for use in a once-a-day diltiazem formulation, which exhibits a dissolution profile, in its broadest ranges, as follows:

a) 0 to 10.3% of the diltiazem is released after 2 hours;

b) 0 to 10.5% of the diltiazem is released after 4 hours;

c) 0 to 15% of the diltiazem is released after 6 hours;

d) 0 to 15% of the diltiazem is released after 8 hours;

e) 4.5% to 24.5% of the diltiazem is released after 14 hours;

f) 41% to 61% of the diltiazem is released after 16 hours; and

g) more than 60% of the diltiazem is released after 18 hours.

See claims 60-70.

Sherman, however, fails to disclose or even suggest the dissolution characteristics of the long lag pellet claimed by the present invention. For example, Sherman discloses 20-45% of diltiazem release at the 6 hour time point. This range is critical according to Sherman's specification, which states that "the amount (of diltiazem) released must exceed 20% after 6 hours" (see page 4, line 5-6). In contrast, the long lag pellet of the present invention exhibits, for example, a range of 0-15% of diltiazem release after 6 hours, which is clearly outside the range disclosed by Sherman. Sherman also discloses "rapid release beads" which are acceptable when exhibiting 90-100% release after the 6 hour time point (see page 6, table 1) or 95% (see page 14, Example 2, Table 2). Again, the long lag pellet of the present invention exhibits, for example, a range of 0-15% of diltiazem release after 6 hours, which is clearly outside the range disclosed by Sherman.

Sherman also discloses that "delayed release beads" are acceptable when exhibiting 30-60% release at the 18 hour time point (see page 6, table 1) or 44% (see page 16, Example 4, Table 4). In contrast, the long lag pellet of the present invention exhibits, for example, a range of more than 60% of diltiazem release after 18 hours, which is clearly outside the range disclosed by Sherman.

Sherman further discloses "intermediate release beads" which release 35-75% of diltiazem after 12 hours (see page 6, Table 1). In contrast, the long lag pellet of the present invention exhibits, for example, a range of 4.5-24.5% of diltiazem release after 14 hours, which is clearly outside Sherman's inherent[1] disclosure of at least 35% after the same time point.

Finally, Sherman discloses a "desired dissolution profile" with an inherent release amount of more than 20% after 8 hours and more than 25% after 14 hours (see page 3, lines 10-18). Sherman's "rapid release beads" also exhibit an inherent release amount of more than 40% after 4 hours, more than 90% release after 8 hours, and more than 90% release after 14 hours (see page 6, Table 1). As discussed above, these ranges are outside the ranges claimed by applicants. Clearly, Sherman fails to disclose a long lag pellet with the dissolution profile claimed by the present invention. Furthermore, Sherman provides no teaching or suggestion to modify the ranges specifically disclosed by Sherman to arrive at the dissolution profile(s) of the present invention. In fact, as the dissolution profiles disclosed in Sherman are stated to be the **"desired"** profiles, Sherman teaches away from the present invention and provides no motivation to one of

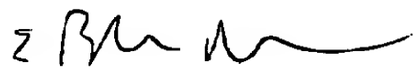
[1] It is well known in the art that the release of an active drug substance from a composition is an on-going process. The amount of active present in its releasing environment is cumulative. In other words, the amount of active drug released for each consecutive time point is inherently deemed the minimum amount from the previous time point.

ordinary skill in the art to deviate from the "desired" dissolution profiles disclosed by Sherman.

Conclusion

In view of the above amendments and remarks, the Applicants respectfully submit that Claims 60-70 are now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,



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Attachm nt 1 to Amendment Filed August 12, 2002
Marked-up Version of Claims 60-70

60. (Amended) A long lag pellet suitable for use in a once-a-day diltiazem formulation comprising a core and a coating layer sufficiently enveloping the core, wherein

1) the [a] core comprises [comprising] an effective amount of diltiazem or a pharmaceutically acceptable salt [, the core] and is [being] substantially free of organic acid; and

2) [where] the long lag pellet substantially exhibits the following dissolution profile when measured according to U.S. Pharmacopia XXII in a type 2 dissolution apparatus at 37°C in 0.1N HCl at 100 rpm:

a) 0 to 10% of the diltiazem is released after 2 hours;

b) 0 to 10% of the diltiazem is released after 4 hours;

c) 0 to 15% of the diltiazem is released after 6 hours;

d) 0 to 15% of the diltiazem is released after 8 hours;

e) 4.5% to 24.5% of the diltiazem is released after 14 hours;

f)41% to 61% of the diltiazem is released after 16 hours; and

g) more than 60% of the diltiazem is released after 18 hours.

61. (Amended) A long lag pellet suitable for use in a once-a-day diltiazem formulation comprising a core and a coating layer sufficiently enveloping the core, wherein

1) the [a] core comprises [comprising] an effective amount of diltiazem or a pharmaceutically acceptable salt [, the core] and is [being] substantially free of organic acid; and

2) [where] the long lag pellet substantially exhibits the following dissolution profile when measured according to U.S. Pharmacopia XXII in a type 2 dissolution apparatus at 37°C in 0.1N HCl at 100 rpm:

a) 0 to 10.3% of the diltiazem is released after 2 hours;

b) 0 to 10.5% of the diltiazem is released after 4 hours;

c) 0 to 10.7% of the diltiazem is released after 6 hours;

d) 0 to 10.9% of the diltiazem is released after 8 hours;

e) 4.5% to 24.5% of the diltiazem is released after 14 hours;

f) 41% to 61% of the diltiazem is released after 16 hours; and

g) more than 60% of the diltiazem is released after 18 hours.

62. (Amended) A once-a-day diltiazem formulation for oral administration comprising a mixture of two types of pellets, one of which is a long lag pellet that comprises a core and a coating layer sufficiently enveloping the core, wherein

1) the [a] core comprises [comprising] an effective amount of diltiazem or a pharmaceutically acceptable salt [, the core] and is [being] substantially free of organic acid; and

2) [where] the long lag pellet substantially exhibits the following dissolution profile when measured according to U.S. Pharmacopia XXII in a type 2 dissolution apparatus at 37°C in 0.1N HCl at 100 rpm:

a) 0 to 10% of the diltiazem is released after 2 hours;

b) 0 to 10% of the diltiazem is released after 4 hours;

c) 0 to 15% of the diltiazem is r leased after 6 hours;

d) 0 to 15% of the diltiazem is released after 8 hours;

e) 4.5% to 24.5% of the diltiazem is released after 14 hours;

f) 41% to 61% of the diltiazem is released after 16 hours; and

g) more than 60% of the diltiazem is released after 18 hours.

63. (Amended) A once-a-day diltiazem formulation for oral administration comprising a mixture of two types of pellets, one of which is a long lag pellet that comprises a core and a coating layer sufficiently enveloping the core, wherein

1) the [a] core comprises [comprising] an effective amount of diltiazem or a pharmaceutically acceptable salt [, the core] and is [being] substantially free of organic acid; and

2) [where] the long lag pellet substantially exhibits the following dissolution profile when measured according to U.S. Pharmacopia XXII in a type 2 dissolution apparatus at 37°C in 0.1N HCl at 100 rpm:

a) 0 to 10.3% of the diltiazem is released after 2 hours;

b) 0 to 10.5% of the diltiazem is released after 4 hours;

c) 0 to 10.7% of the diltiazem is released after 6 hours;

d) 0 to 10.9% of the diltiazem is released after 8 hours;

e) 4.5% to 24.5% of the diltiazem is released after 14 hours;

f) 41% to 61% of the diltiazem is released after 16 hours; and

g) more than 60% of the diltiazem is released after 18 hours.

64. (Amended) A long lag pellet according to claims 60 through 63 [91 through 94] where 14.5% to 24.5% of the diltiazem is released after 14 hours.

65. (Amended) A long lag pellet according to claims 60 through 63 [91 through 94] where 51% to 61% of the diltiazem is released after [14] 16 hours.

66. (Amended) A long lag pellet according to claims 60 through 63 [91 through 94] where 41% to 51% of the diltiazem is released after [14] 16 hours.

67. (Amended) A long lag pellet according to claims 60 through 63 [91 through 94] where 14.5% to 24.5% of the diltiazem is released after 14 hours and 51% to 61% of the diltiazem is released after [14] 16 hours.

68. (Amended) A long lag pellet according to claims 60 through 63 [91 through 94] where 14.5% to 24.5% of the diltiazem is released after 14 hours and 41% to 51% of the diltiazem is released after [14] 16 hours.

69. (Amended) A long lag pellet according to claims 60 through 63 [91 through 94] where

a) 0-10.3% of the diltiazem is released after 1 hour;

b) 0-11.3% of the diltiazem is released after 10 hours; and

c) 0-13.1% of the diltiazem is released after 12 hours

70. (Amended) A long lag pellet according to claims 60 through 63 [91 through 94] where

a) 0-10.3% of the diltiazem is released after 1 hour;

b) 0-11.3% of the diltiazem is released after 10 hours;

c) 0-13.1% of the diltiazem is released after 12 hours;

d) 14.5% to 24.5% of the diltiazem is released after 14 hours; and

e) 51% to 61% of the diltiazem is released after [14] 16 hours.

Attachment 2 t Amendment Filed August 12, 2002
Marked-up Version of Specification

At page 1, line 6, -- "This application is a continuation of application Serial No. 09/447,642, filed November 23, 1999, now [pending] U.S. Patent No. 6,214,385, which is a continuation of application Serial No. 09/287,904, filed April 7, 1999, now U.S. Patent No. 6,033,687, which is a continuation of application Serial No. 09/169,172, filed October 9, 1998, which is a continuation of application Serial No. 08/814,602, filed March 10, 1997, now U.S. Patent No. 5,834,024, which is a continuation-in-part of application Serial No. 08/369,100, filed January 5, 1995, now abandoned."--

[redacted] 308 6916

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*** RX REPORT ***
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RECEPTION OK

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